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Letter to the Editors

Negligible impact of a *HTR1A* gene promoter variant on suicidal behavior

Dear Editors,

I have read with great interest the recent meta-analysis of rs6295 effects on suicidal behavior conducted by Angles et al.[1] Praise to the authors for having rigorously selected eligible studies prior to embarking on their analysis. The message is clear. Unfortunately, the calculations are in error as alleles were muddled in one of the four investigations on which the random effects model was based: Lemonde et al.[2] examined the transcribed DNA strand, whereas the remaining studies refer to the anti-parallel strand. When this is overlooked, G and C alleles are exchanged and the G allele becomes risk-enhancing rather than protective. Even if the data in question are dropped on the grounds of heterogeneity, I have counted four additional studies of which at least one[3] warrants inclusion in the model. After correcting for these confounders, the pooled odds ratios obtained are 0.86 (0.7-1.2) and 0.97 (0.8-1.1), respectively (Figure 1). No significant association with suicidal behavior emerges which is in line with a further, more recent publication.[4]

The main concern with present and past research in the field remains, however, the lack of adequate specification of genetic exposure that precludes all verifications of this kind. A growing number of studies has referred to rs6295 without providing experimental details on the DNA strand amplified and the allele actually called. Literally, such data make little sense and cannot be used for aggregating results across examinations to increase statistical power.[5] It appears unlikely, therefore, that larger samples will shed more light on the role of rs6295 in candidate phenotypes unless genotyping procedures are routinely reported in full detail to help decrypt this information.

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Disclosure

Philipp G. Sand

Employment: *University of Regensburg, Germany.*

* *Modest*

** *Significant*

*** *Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*

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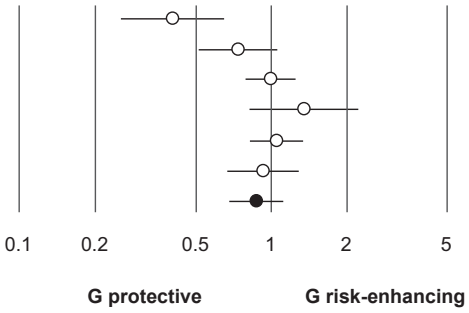
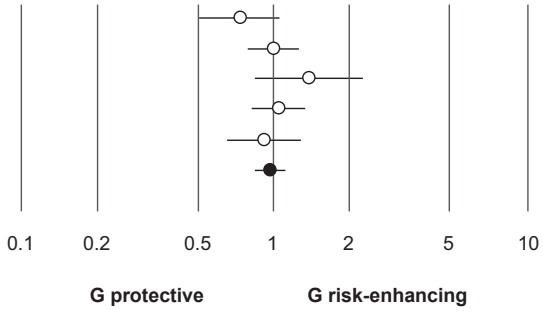
(a)

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Lemonde et al.[2]	0.402	0.253	0.638	-3.865	0.000
Serretti et al.[6]	0.734	0.511	1.055	-1673	0.094
Serretti et al.[6]	0.993	0.787	1.254	-0.055	0.956
Sawiniec et al.[3]	1.364	0.833	2.232	1.233	0.218
Videtic et al.[7]	1.034	0.802	1.333	0.259	0.796
Yoon et al.[8]	0.920	0.658	1.286	-0.488	0.626
Random effects model	0.866	0.670	1.118	-1.103	0.270



(b)

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Serretti et al.[6]	0.734	0.511	1.055	-1673	0.094
Serretti et al.[6]	0.993	0.787	1.254	-0.055	0.956
Sawiniec et al.[3]	1.364	0.833	2.232	1.233	0.218
Videtic et al.[7]	1.034	0.802	1.333	0.259	0.796
Yoon et al.[8]	0.920	0.658	1.286	-0.488	0.626
Random effects model	0.973	0.842	1.126	-0.363	0.716



Circles and horizontal lines correspond to the study-specific OR and 95% confidence intervals (CI). The filled circle represents the pooled OR under a random effects model.

Figure 1 Forest plots of odds ratios (OR) for the rs6295 G allele assuming a codominant mode of inheritance with (a) and without (b) the initial study by Lemonde et al.[2]

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Carta aos Editores

Impacto desprezível de uma variante do gene promotor *HTR1A* sobre o comportamento suicida

Prezados Editores,

Li com grande interesse a recente metanálise dos efeitos do rs6295 sobre o comportamento suicida, realizada por Angles *et al*.[1] Meus cumprimentos aos autores por terem selecionado com rigor os estudos elegíveis antes de proceder a sua análise. A mensagem é clara. Infelizmente, os cálculos estão incorretos, pois os alelos foram trocados em uma das quatro investigações em que se baseou o modelo de efeitos randômicos. Lemonde *et al*.[2] examinaram a hélice do DNA transcrito, enquanto que os demais estudos se referem à hélice anti-paralela. Quando isso não é levado em consideração, os alelos G e C são trocados e o alelo G passa a aumentar o risco em vez de se mostrar protetor. Ainda que os dados em questão sejam abandonados em razão da heterogeneidade, eu contei pelo menos quatro outros estudos, dos quais pelo menos um[3] merece ser incluído no modelo. Depois de se corrigir quanto a esses fatores de confusão, as razões de chance agrupadas obtidas são de 0,86 (0,7-1,2) e 0,97 (0,8-1,1), respectivamente (Figura 1). Não emerge uma associação significativa com o comportamento suicida, o que está de acordo com outra publicação mais recente.[4]

O principal interesse das pesquisas atuais e anteriores no campo, todavia, continua a ser a falta de especificação adequada da exposição genética, que impede toda e qualquer verificação desse tipo. Um número crescente de estudos têm se referido ao rs6295 sem fornecer detalhes experimentais sobre a hélice de DNA amplificada e o alelo efetivamente designado. Esses dados literalmente fazem pouco sentido e não podem ser usados para se agregar resultados através de exames para se aumentar o poder estatístico.[5] Parece improvável, portanto, que amostras maiores vão lançar mais luz sobre o papel do rs6295 em fenótipos candidatos, a não ser que os procedimentos de determinação do genótipo sejam relatados rotineiramente com todos os detalhes para ajudar a se decifrar essas informações.

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Declarações

Philipp G. Sand

Emprego: *University of Regensburg, Alemanha.*

** Modesto*

*** Significativo.*

**** Significativo: Valores dados à instituição do autor ou a um colega por uma pesquisa em que o autor tem participação, não diretamente ao autor. As fontes de financiamento não tiveram nenhuma participação no desenho experimental do estudo,na coleta, análise e interpretação dos dados, na redação do relatório e na decisão de submeter o artigo à publicação.*

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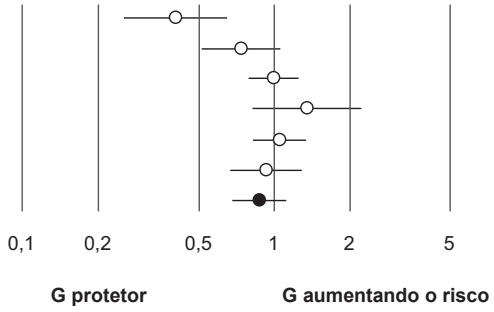

(b)

	Razão de chance	Limite inferior	Limite superior	Valor Z	Valor p
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Serretti et al.[6]	0,993	0,787	1,254	-0,055	0,956
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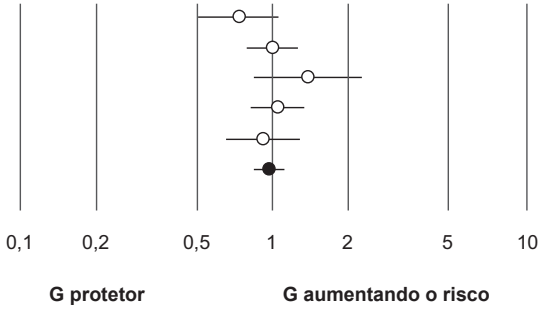

Círculos e linhas horizontais correspondem à RC e ao intervalo de confiança (IC) de 95% específicos do estudo. O círculo cheio representa a RC agrupada segundo um modelo de efeitos randômicos.

Figura1 Representação Foresta da razão de chance (RC) para o alelo G rs6295, supondo-se ium modo de herança co-dominante, com (a) e sem (b) o estudo inicial de Lemonde et al.[2]

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